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Allogeneic Hematopoietic Cell Transplantation for Chronic Myelofibrosis in Australia and New Zealand: Older Recipients Receiving Myeloablative Conditioning at Increased Mortality Risk

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This retrospective registry analysis examined predictive factors for outcome in 57 patients who underwent allogeneic or syngeneic hematopoietic cell transplantation (HCT) for chronic myelofibrosis (CM), either primary (n = 49) or following an antecedent condition (n = 8), reported to the Australasian Bone Marrow Transplant Registry (ABMTRR) between 1993 and 2005. During the 6 years 2000 to 2005, 40 HCTs were performed for CM compared with 17 in the 7 years 1993 to 1999. Twenty-four recipients (42%) were age 50 or over at transplantation; all of these patients were transplanted after 1997, and 15 were given reduced intensity conditioning (RIC) pretransplantation. The cumulative incidence of transplantation-related mortality was 18% at 100 days and 25% at 1 year posttransplantation. Up to 1 year posttransplantation 16 patients died, with the most common causes being infection (n = 6) and graft-versus-host disease (GVHD) (n = 5). A total of 27 patients survived for 3 years or longer posttransplantation. None of these patients required regular red blood cell transfusions, and of the 17 who had not had splenectomies, none had detectable splenomegaly. Twelve patients had no detectable bone marrow fibrosis, 7 had grade 1 fibrosis, and in 8 patients no information was available. The overall survival (OS) probability for all patients was 72% at 1 year and 58% at 5 years posttransplantation. Patients age 50 and over who received myeloablative conditioning fared poorly, with 1-year overall actuarial survival of 44% compared with 77% for all other patients ($P = .007$). In multivariate analysis, age 50 years and over at transplantation was the only significant independent unfavorable risk factor for survival post-HCT (hazard ratio 2.71, 95% confidence interval 1.16-6.34, $P = .02$). This study shows a clear increase in annual numbers of allogeneic HCT performed for CM in Australia and New Zealand in recent years. Five-year survival was favorable compared with international studies, but for older recipients who received myeloablative conditioning, mortality risk was elevated.

Biol Blood Marrow Transplant 18: 302-308 (2012)

KEY WORDS: Allogeneic hematopoeitic cell transplantation, Chronic myelofibrosis

INTRODUCTION

Chronic myelofibrosis (CM) is a rare chronic myeloproliferative disorder characterized by marrow fibrosis, splenomegaly because of extramedullary hematopoiesis, leukoerythroblastic blood changes, and tear-drop deformities of red blood cells [1,2]. The primary pathogenetic mechanism is a clonal stem cell disorder that results in ineffective erythropoiesis, dysplastic megakaryocyte hyperplasia, and an increase in the ratio of immature granulocytes to total granulocytes [1]. This disease has also been termed agnogenic myeloid metaplasia [2,3] and myelofibrosis with myeloid metaplasia [1]. Myelofibrosis may be primary or may develop following an antecedent hematologic disorder such as essential thrombocythaemia or polycythemia rubra vera [1,2].

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Financial disclosure: See Acknowledgments on page 307.

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Received March 29, 2011; accepted May 4, 2011

1083-8791/$36.00
doi:10.1016/j.bbmt.2011.05.003

The trilineage proliferation in chronic myelofibrosis is clonal and has a stem cell origin [1]. Cellular changes include increases in the number of stromal cells and in the levels of extracellular matrix proteins, increased angiogenesis, and osteosclerosis. These changes in the microenvironment of the bone marrow coexist with alterations in the cellular and extracellular levels of various cytokines that have fibrogenic, angiogenic, or osteogenic potential [1].

Many cytogenetic abnormalities are associated with CM including 13q-; 20q-; +8; and abnormalities of chromosomes 1, 7, and 9 [4]. The JAK2-V617F mutation occurs in approximately 50% of patients diagnosed with CM [5,6] and has been associated with poorer survival in some studies, although this association is still controversial [7]. Indicators of poor prognosis include increased age and anemia at diagnosis [1,8-10]. CM may undergo malignant transformation to acute myeloid leukemia (AML) [1].

Allogeneic hematopoietic cell transplantation (HCT) is the only potentially curative option currently available for CM [2,11]. A number of studies have now been published on the outcome of allogeneic HCT for this disease [2,12-22]. In the current study, accumulated results of 57 Australian and New Zealand HCT for CM performed from 1993 to 2005 are reviewed, highlighting changes in activity, similarities, and differences to published international experience.

PATIENTS AND METHODS

Study Design

Allogeneic HCT recipients were selected for this study from the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR) database, which captures details on more than 95% of HCTs performed in Australia and New Zealand [23]. Patient consent for data to be recorded in the ABMTRR is obtained by individual participating institutions. This study was approved by the ABMTRR Steering Committee.

Patients were included if they underwent allogeneic or syngeneic HCT for the indication of chronic myelofibrosis in Australia or New Zealand between 1993 and 2005, including those in whom the CM was secondary to polycythemia rubra vera or essential thrombocythemia. Patients transplanted for AML who had progressed from CM were not included.

A detailed questionnaire was distributed to centers in November 2006, asking for information on the transplant donor and recipient, plus copies of pathology documentation. The responses were reviewed centrally for further coding by ABMTRR statistical staff and clinicians. Patient data used in this analysis comprised the most current information available as of December 31, 2009.

Definitions

Day of neutrophil engraftment was defined as the first of 3 consecutive days when the blood neutrophil count was equal to or higher than 0.5×10^9/L, and day of platelet engraftment was defined as the first day when the blood platelet count was higher than 20×10^9/L and there had been no platelet transfusions in the previous 7 days. Median engraftment was calculated by cumulative incidence methods using death without engraftment as a competing risk. Patients and donors were considered HLA-identical if they were matched at 6 of 6 A-, B-, and DR-loci at the DNA level if available, otherwise the serologic level. HLA-typing data was reported by each individual center; information on additional HLA loci was not available because of the retrospective nature of the data collection.

Transplant-related mortality (TRM) was calculated as the cumulative incidence of deaths posttransplantation from causes other than relapse and persistent disease, which were treated as competing risks. Patients were considered evaluable for engraftment and acute graft-versus-host disease (aGVHD) if they survived at least 21 days after HCT. GVHD was classified as acute when occurring up to 100 days posttransplantation, and chronic after this time. Grading of acute GVHD (aGVHD) was performed according to criteria used by the Center for International Blood and Marrow Research (CIBMTR) [24]. The cumulative incidence of GVHD was calculated by treating death from causes other than GVHD as a competing risk. Performance status at transplantation was defined as good (Karnofsky performance scale of 80% or greater, or ECOG performance status of 0-1), or poor otherwise. Relapse was defined as the reappearance of morphologic criteria of myelofibrosis after initial clearing of the marrow. Disease-free survival (DFS) was defined as a continuous hematologic remission after transplantation. Overall survival (OS) was defined as the time from transplantation to death or last contact.

The grading of bone marrow fibrosis was performed in accordance with the system developed by Barosi et al. [25]. Marrow biopsies were taken pretransplantation and at or near 3 months posttransplantation. Patients were classified as "low," "intermediate," or "high" risk using the method of Dupriez [3]. Six of the patients included in this study were analyzed in a previous investigation of allogeneic HCT for CM using reduced-intensity conditioning (RIC) at a single institution [26].

Analysis Methods and Software Used

All analyses were performed using Stata statistical software Release 10 (Statacorp LP, College Station, TX). Differences between groups were assessed using

either a Mann-Whitney *U* test for continuous variables or a chi-squared test or Fisher exact test as appropriate for categoric variables. OS and DFS were calculated using Kaplan-Meier product limit estimates, and differences between groups were assessed with the log-rank test.

Multivariate Cox regression analysis was performed to establish the significant factors affecting incidence of aGVHD and OS. The following variables were tested for significant effects in Cox regressions: year of transplantation in 1993-1999 compared with 2000-2005, recipient age (50 years and older), length of time from diagnosis to transplantation, donor age and sex, donor HLA compatibility, donor relationship to recipient, stem cell source, type of pretransplantation conditioning, performance status at transplantation, red blood cell transfusion dependency, splenectomy status at transplantation and level of bone marrow fibrosis pretransplantation.

RESULTS

Data for 57 patients transplanted between June 1993 and November 2005 at 15 centers (13 Australia, 2 New Zealand) were received and analyzed, representing all reported Australasian allogeneic HCT activity for CM over this time. Six centers submitted 1 transplantation each, whereas the maximum number at 1 center was 14. One recipient received an allogeneic transplantation following an autograft for CM; all others were first allogeneic transplantations. Forty-nine patients were treated for primary myelofibrosis, whereas 8 had antecedent conditions of essential thrombocythemia (n = 3) or polycythemia rubra vera (n = 5). During the 7 years 1993 to 1999, 17 HCTs were performed (2.4 per year), and in the 6 years 2000 to 2005, 40 were performed (6.7 per year; Figure 1). To put these figures in perspective, the total combined population of Australia and New Zealand was 21.4 million people in 1993 and 24.6 million in 2005. Most (39, 68%) of the recipients were male (Table 1). The median length of time from diagnosis to transplantation was 15 months for patients age under 50, compared with 37 months for those age 50 and above ($P = .04$), and 22 months overall. Twenty-four recipients (42%) were age 50 or over at transplantation; all of these patients were transplanted after 1997, and 15 were given RIC pretransplantation. The majority of recipients (43, 75%) received hematopoietic cells from HLA-identical siblings, including 4 syngeneic (identical twin) transplants; the remaining 13 received grafts from adult volunteer unrelated donors.

Two-thirds of the patients (39, 68%) received stem cells collected from peripheral blood (PBSC). Twenty-two patients were given cyclophosphamide/total body irradiation (TBI) conditioning (Table 2); of these, 18 were age less than 50. Another 16 were given busulphan/cyclophosphamide (Bu/Cy); 13 of these patients were age under 50. Seventeen patients had RIC regimens; 15 of these patients were age 50 or over, and all RIC transplantations were performed later than

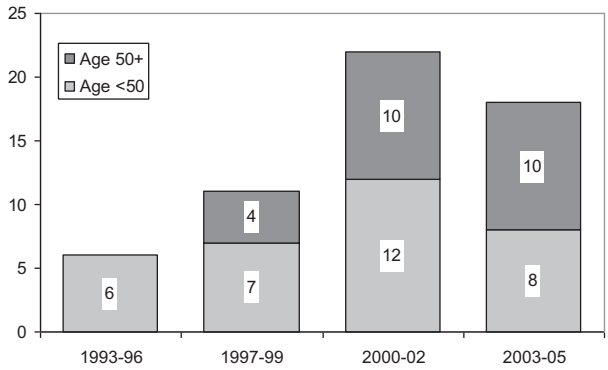

Figure 1. Numbers of allogeneic HCT for chronic myelofibrosis in Australia and New Zealand, 1992-2005, by recipient age. Numbers of allogeneic HCT for chronic myelofibrosis have increased in recent years, particularly from 2000.

Table 1. Patient and Donor Characteristics

Variable	Categories	Values
Number of patients	n	57
Patient sex	M:F	39:18
Patient age	Years: median (range)	47 (16-71)
Patient age range	<40	10
	40-49	23
	50-59	16
	60 +	8
Length of time diagnosis–transplantation	Months: median (range)	22 (2-192)
Compounds used in prior treatment	None	19
	Hydroxyurea only	26
	Hydroxyurea + other (1)	7
	Other compounds (2)	5
Donor relation and HLA match	HLA-identical sibling	39
	Identical twin	4
	Other relative	3
	Unrelated	11
Donor sex	M:F	36:21
Donor age	Years: median (range)	46 (26-70)
Stem cell source	Marrow	17
	Peripheral blood	39
	Marrow + PB	1
Performance status before conditioning	Good (Karnofsky 80+)	48
	Poor (Karnofsky <80)	9
Red cell transfusion dependency before transplant	Dependent	29
	Not dependent	22
	Unknown	6
Grade of BM fibrosis before transplantation	MF-1	9
	MF-2	19
	MF-3	20
	Unknown	9
Dupriez score	Good	25
	Intermediate	18
	Poor	13
	Unknown	1

1 indicates busulphan, glivec, interferon, anagrelide, thioguanine; 2, cytarabine/etoposide/daunorubicin, cytarabine/fludarabine, interferon, oxymethalone; BM, bone marrow.

Table 2. Transplantation Characteristics

Variable	Categories	Values
Splenomegaly/ splenectomy	No splenomegaly or splenectomy	7
	Splenomegaly, no splenectomy	21
	Splenomegaly, splenectomy	29
CMV status	Donor and recipient +ve	26
	Donor −ve, recipient +ve	11
	Donor +ve, recipient −ve	9
	Donor and recipient −ve	11
Pretransplantation conditioning	Cyclophosphamide + TBI (1)	22
	Busulphan + Cyclophosphamide	16
	Other myeloablative (2)	2
	Fludarabine + Melphalan (RIC) (3)	10
	Fludarabine + TBI (RIC) (3)	4
	Other RIC (3)	3
GVHD prophylaxis	CSP (4) + MTX (5)	21
	CSP + MTX + corticosteroids	10
	CSP + MMF (6)	3
	Other combinations	19
	None	4
Hemoglobin level before conditioning	Less than 100 g/L	24
	100 g/L or higher	33
Nucleated cells given ($\times 10^8$/kg)	Median (range)	7.0 (1.2- 22.5)
$CD34^+$ cells given ($\times 10^6$/kg)	Median (range)	4.9 (1.3- 23.9)
Median day of engraftment	Neutrophils	16
	Platelets	30
Adverse events posttransplantation	Interstitial pneumonitis	2
	Veno-occlusive disease	4
	Hemorrhagic cystitis	4
	CMV infection	7

1 indicates total body irradiation; 2, cyclophosphamide only, LACE + ATGAM; 3, reduced-intensity conditioning; 4, cyclosporin; 5, methotrexate; 6, mycophenolate mofetil.

1999. Fifty patients had splenomegaly pretransplantation; of these, 29 had a splenectomy.

More than one-half of recipients (31, 54%) received cyclosporine (CSP) and methotrexate (MTX), or these 2 compounds plus corticosteroids, as GVHD prophylaxis (Table 2); the 4 syngeneic recipients received no GVHD prophylaxis.

Cytogenetic abnormalities in marrow samples were unknown or not able to be tested for in 34 patients; another 14 had no abnormalities listed. Two patients had abnormalities involving deletions at the long arm of chromosome 13 (13q-), 3 patients had abnormalities involving deletions at the long arm of chromosome 20 (20q-) and 3 had abnormalities involving trisomy at chromosome 8 (+8). JAK2 mutation incidence was not available for these patients, because this abnormality was not tested during the time frame of the study.

Forty-eight patients (84%) achieved neutrophil engraftment posttransplantation, and the median time was 16 days. Median time to neutrophil engraftment was 15 days for PBSC recipients compared with 20 days for those who received marrow grafts ($P = .08$), and 15 days for patients who had splenectomy compared with 19 days for those who had not ($P = .2$). Forty-one patients (72%) achieved platelet engraftment posttransplantation, with a median time of 30 days. Rates of neutrophil and platelet engraftment did not vary significantly between different recipient age groups, cell doses, or presence of osteomyelosclerosis at transplantation. Seven patients did not engraft (ie, neither neutrophil nor platelet engraftment achieved). Five of these patients died within 30 days posttransplantation from severe immediate posttransplantation complications and were thus not evaluable for engraftment (3 from infection, 1 from interstitial pneumonitis, 1 from hepatic veno-occlusive disease), another died within 1 year, and the remaining patient was recorded as alive at 3.9 years posttransplantation.

Pretransplantation, 29 (51%) patients were red blood cell transfusion dependent, whereas by 30 days posttransplantation this had dropped to 18 (35% of surviving patients), and then to 7 (15% of surviving patients) at 100 days posttransplantation. Twenty patients had bone marrow fibrosis graded at MF-3 pretransplantation. Of these, 13 showed some improvement (7 to MF-2, 6 to MF-1) at 6 months posttransplantation, whereas 1 patient remained MF-3, MF status was not evaluable in another 2 patients because of early death, and was unknown in another 4. Of 26 patients whose level of bone marrow fibrosis was evaluable both before and 3 months after transplantation, 15 had lower levels of fibrosis post- than pretransplantation, in 8 the level of fibrosis remained the same, and in 3 the level of fibrosis was worse posttransplantation. All 3 of the patients whose fibrosis increased posttransplantation had engrafted successfully, with neutrophils and platelets recovering by day 20 posttransplantation. These 3 patients were age 40, 62, and 63, and all had good performance status when transplanted.

A total of 27 patients survived for 3 years or longer posttransplantation. At or close to 3 years posttransplantation, none of these patients required regular red blood cell transfusions, and of the 17 who had not had splenectomy, none had detectable splenomegaly. Twelve patients had no detectable bone marrow fibrosis, 7 had bone marrow fibrosis grade 1, and in 8 patients the level of bone marrow fibrosis was unknown. Twenty-two patients had normal blood counts, 2 had low platelet levels, 1 had a low hemoglobin level, and for 2 patients' blood counts had not been recorded.

The overall cumulative incidence of aGVHD Grade II and above was 37% at 100 days posttransplantation. Recipients with donors other than HLA-identical siblings experienced higher levels of aGVHD Grade II+ (50% vs 33%, $P = .08$). Seven patients relapsed between 160 and 560 days posttransplantation; of these, 6 subsequently died, all within 2.2 years posttransplantation, whereas the remaining relapsed patient was recorded as alive 1.2 years posttransplantation. The

Table 3. Primary Cause of Death up to 1-Year Post-transplantation

Primary cause	Number
Infection	6
Graft-versus-host disease (GVHD)	5
Disease persistence/recurrence	2
Interstitial pneumonitis (IP)	1
Organ failure	1
Veno-occlusive disease (VOD)	1
Total deaths	16

cumulative incidence of relapse was 9% at 1 year and 12% at 2 years posttransplantation, whereas that of TRM was 18% at 100 days and 25% at 1 year posttransplantation. Recipients age 50 and over experienced higher levels of TRM (38% vs 15% at 1 year, $P = .06$). The most common causes of death up to 1 year posttransplantation were infection (n = 6) and GVHD (n = 5, Table 3). There were 7 more deaths between 1 and 5 years posttransplantation; 4 of these were from disease recurrence. None of the 4 syngeneic recipients either relapsed or experienced aGVHD. At time of analysis, 3 syngeneic recipients were alive at 5, 7, and 16 years posttransplantation, whereas 1 had died of organ failure within the first year posttransplantation.

The median length of follow-up for surviving patients at analysis was 6.0 years, with a minimum of 1.2 years. OS probability for the entire group was 72% at 1 year and 58% at 5 years posttransplantation, whereas 5-year DFS was 57% (Figure 2). OS probability was significantly higher for recipients age less than 50 at transplantation than for those age 50 and over (79% at 2 years posttransplantation vs 45%, $P = .02$, log-rank test). Patients conditioned with Cy and TBI had lower OS than all other patients (59% at 2 years posttransplantation vs 68%, $P = .2$). OS probability was not significantly affected by stem cell source, hemoglobin level at transplantation, year of transplantation, length of time from diagnosis to transplantation, Dupriez Score [3], level of bone marrow fibrosis, performance status, or red cell transfusion dependency status at transplantation. Prior splenectomy had no effect on survival outcome in univariate survival analysis.

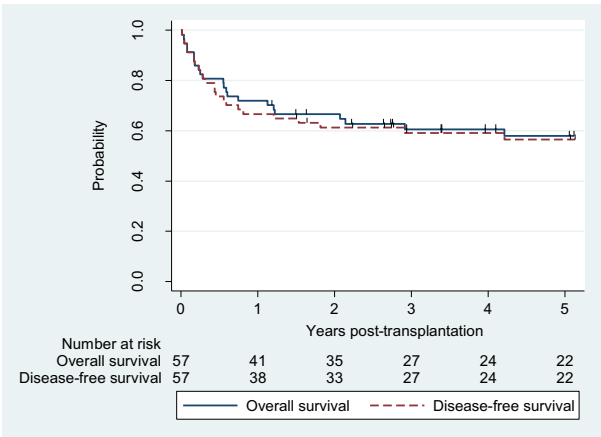

Figure 2. Overall survival (OS) and disease-free survival (DFS) probability. At 5 years posttransplantation, OS was 58% and DFS was 57%.

Of the 15 recipients age 50 or over who received RIC, 7 had died by time of analysis and their 2-year OS probability was 53%. In contrast, of the 9 recipients age 50 and over who had myeloablative conditioning regimens, 7 died before 3 years posttransplantation and their 1-year OS probability was 44% compared with 77% for all other recipients ($P = .007$). Age 50 years and over at transplantation was the only significant independent unfavorable risk factor for both OS post-HCT (hazard ratio [HR] 2.71, 95% confidence interval [CI] 1.16-6.34, $P = .02$) and DFS (HR 3.00, 95% CI 1.30-6.93, $P = .01$). After allowing for age group, the effect of RIC on OS appeared to be beneficial (HR 0.45, 95% CI 0.16-1.24, $P = .10$).

DISCUSSION

This study shows that allogeneic HCT is a potentially curative treatment for CM, leading to long-term remission for a relatively large proportion of patients. The findings highlight the increased role of RIC in HCT for CM in recent years. The annual numbers of allogeneic HCT for CM in Australia and New Zealand almost tripled between 1993-1999 (2.4 HCT per year) and 2000-2005 (6.7 HCT per year). The majority of this increase was because of older patients who were being transplanted, most of whom received RIC. The time from diagnosis to transplantation was significantly longer for patients age 50 and above compared with those who were younger, indicating that physicians may have delayed transplantation of older patients until major progression of the underlying disease.

The age and sex of the patients in this study (68% male, median age 46 years) were similar to those in other major studies [2,11,12,15,21,27]. There was a clear reduction in the posttransplantation average level of bone marrow fibrosis and dependency on red blood cell transfusions among the patients in this study. Of those who survived for 3 years or more posttransplantation, none were red blood cell transfusion dependent, and none had a recorded bone marrow fibrosis level >1.

TRM at 1 year posttransplantation was higher for patients age 50 years and above (38%) than for those age under 50 (15%, $P = .06$). The overall TRM of 25% at 1 year posttransplantation was similar to that reported by other major studies [2,11,15,19,21,27]. In contrast, the cumulative incidence of relapse of 9% at 1 year and 12% at 2 years posttransplantation was low compared with other large studies [15,21]. The OS probability at 5 years posttransplantation (58%) compared favorably with that stated in studies

by Guardiola et al. (47%) [2] and Ballen et al. (30% to 40%) [21], and was lower than only that stated by Kerbuay et al. [12] (61% at 7 years). Previous studies have found factors that adversely affected survival, which included hemoglobin levels of 100 g/L or less pretransplantation and prior osteomyelosclerosis [2], and factors associated with improved survival included younger age at transplant, decreased morbidity score, high platelet count at transplantation, and the use of Bu/Cy conditioning [12]. The current analysis found that myeloablative conditioning regimens were associated with younger age and that RIC was used almost exclusively for patients age 50 years and over; conditioning type alone did not have a significant effect on outcome. Among the patients in this study age 50 and above, those receiving RIC regimens had similar long-term survival to younger patients, whereas those receiving myeloablative conditioning regimens fared poorly. However, the only significant adverse factor for posttransplantation survival found in multivariate analysis in this study was patient age of 50 and above ($P = .02$).

This analysis demonstrates favorable results for patients transplanted for CM in Australia and New Zealand compared with other international studies, with similar levels of TRM to those reported by other studies but comparatively low rates of relapse and high overall OS. This study provides evidence that older patients transplanted for CM with RIC regimens experience better outcomes than those transplanted with myeloablative regimens. Future research should clarify the effect of the presence of the JAK2 mutation on posttransplantation survival and the role of RIC in transplantation conditioning for CM patients.

ACKNOWLEDGMENTS

The authors sincerely thank Leonie Wilcox and Donna Aarons for their dedication and expertise in maintaining the ABMTRR database. We thank the following clinicians and staff at their centers for participating in this study: Andrew Spencer (Alfred Hospital), Peter Browett (Auckland Hospital), John Carter (Wellington Hospital), Bik To (Royal Adelaide Hospital), Karin Tiedemann (Royal Children's Hospital Melbourne), Chris Arthur (Royal North Shore Hospital), John Gibson (Royal Prince Alfred Hospital), Paul Cannell (Royal Perth Hospital), Ian Irving (Townsville Hospital), and John Bashford (Wesley Medical Centre). We also thank clinical and data management staff at all centers that correspond with the ABMTRR for their continuing and unstinting efforts. The ABMTRR is grateful to the BMT Network NSW, The Arrow Bone Marrow Transplant Foundation, St. Vincent's Hospital Darlinghurst, and the Australian Bone Marrow Donor Registry for their support.

Financial disclosure: The authors declare no financial relationship with any organizations that have a direct financial interest in the subject matter discussed in the submitted paper.

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